Summary Basis for Regulatory Action

Date	17 January 2013
From	Nancy Kirschbaum, PhD, Committee Chair
Subject	Summary Basis for Regulatory Action
BLA #	STN 125416/0
Applicant	Octapharma
Date of Submission	23 December 2011
PDUFA Goal Date	21 January 2013
Proprietary Name/Established Name	Octaplas™/Pooled Plasma (Human), Solvent Detergent Treated
Dosage form	Liquid frozen, 200 ml
Proposed Indication(s)	• Replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease, and in patients undergoing cardiac surgery or liver transplantation. • For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)
Recommended Action	Approval
Signatory Authority Action	Jay Epstein, MD_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum* Mary Anne Malarkey_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum*

Material Reviewed/ Consulted: Specific documentation used in developing the SBRA Reviewer Name - Document(s)	
Clinical Review	Mitchell Frost, MD
Clinical Pharmacology	Harold Boxenbaum, PhD; Iftekar Mahmood, PhD

Material Reviewed/ Consulted: Specific documentation used in developing the SBRA Reviewer Name - Document(s)	
Review	
Statistical Review	Renee Rees
CMC Review	Mikhail Ovanesov, PhD; Ze Peng, PhD; Nancy Kirschbaum, PhD; Jie He
Pharmacology/ Toxicology Review	M. Keith Wyatt, PhD; Anne Pilaro, PhD
Bioresearch monitoring Review	Christine Drabick
Establishment Inspection Report	Anthony Lorenzo, Jie He, Nancy Kirschbaum, PhD
Advisory Committee Transcript	20 September 2012
Other	1. Svae T-E, Svae-Neisser A, Bailey A, Reichl H, Biesert L, Schmidt T, Heger, A, Römisc J. Prion safety of transfusion plasma and plasma-derivatives typically used for prophylactic treatment. (2008) Transfusion and Apheresis Science 39: 59 – 67 2. Hellstern P, Sachse H, Schwinn H, Oberfrank K. Manufacture and *in vitro* characterizat of a solvent/detergent treated human plasma. (1992) Vox Sanguinis 63: 178 – 185 3. Baylis SA, Hanschmann K-M, Blümel J, Nübling. Standardization of HEV NAT based assays: an initial study to evaluate a panel of HEV strains and investigate laboratory performance 4. -----(b)(4)----------

1. Introduction

Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) has submitted an original biologics license application (BLA) for Pooled Plasma (Human), Solvent Detergent Treated for transfusion. The intended commercial product is a frozen, sterile, pyrogen-free, solvent/detergent treated (1% tri-n-butyl phosphate/ 1% octoxynol), pooled human plasma product filled in 200 ml doses into 300 ml polyvinyl chloride (PVC) plasma bags. Plasma pools of 380 L for product manufacture may comprise up to 630 individual units -------(b)(4)--------- 1,520 -----(b)(4)---------- plasma -----(b)(4)---------- plasma sources. The proprietary name of the US marketed product will be Octaplas™. The same product is currently marketed outside the US under the proprietary name OctaplasLG, which was the name used for reference in the original BLA.

2. Background

Octaplas™, Pooled Plasma (Human), Solvent Detergent Treated was developed for US market under IND 13956. Octaplas™ is a modified version of Octaplas®, marketed in Europe since 1992. The rationale for product development was to provide standardized, cell free human plasma for transfusion with improved viral safety compared to Fresh Frozen Plasma (FFP). Improved viral safety regarding enveloped viruses has been achieved through incorporation into the manufacturing process of a solvent/detergent (S/D) treatment step validated to inactivate relevant enveloped viruses, while preserving the activity of relevant plasma proteins.

Octapharma has produced and studied five generations of S/D treated pooled human plasma products, all of which have similar manufacturing processes and comparable biochemical properties. Table 1 provides a summary of product development and marketing history.

Table 1: Product Development and Marketing History

Generation	Name	Presentation	ABO Specific	LG column	Commercial Status
G-1	Octaplas®	Lyophilized	Yes	No	No longer marketed
G-2a	Octaplas®	Liquid frozen	Yes	No	Marketed outside US since 1992
G-2b	OctaplasLG/ Octaplas™	Liquid frozen	Yes	Yes	Marketed outside US since 2009
G-3a	Uniplas	Liquid frozen	No	No	---(b)(4)---
G-3b	UniplasLG	Liquid frozen	No	Yes	-----(b)(4)-----

A significant amount of clinical and manufacturing experience exists for the generation 2a product, Octaplas®. Octaplas® is an ABO blood group specific product with an S/D treatment time of 4 – 4.5 hours. Since its first entry into commercial distribution in Europe, more than 2 million patients have been treated with over 6.5 million bags. Today, it is approved in 26 authorities worldwide. Octaplas™ manufacture has incorporated two changes to the process for Octaplas®: (1) reduction of S/D treatment time to 1 – 1.5 hr to increase the levels of Protein S and alpha-2-plasmin inhibitor and (2) addition of a ligand affinity column designed to remove

prion protein (PrP^{Sc}) infectivity, the causative agent of Creutzfeld Jakob Disease (CJD) and variant CJD (vCJD). Octaplas™ was first approved in Germany in 2009 with current, additional approvals in Australia, United Kingdom, Belgium, Finland, Ireland, Luxembourg, The Netherlands, Sweden, Portugal and Switzerland. Uniplas and UniplasLG are non-ABO blood group specific products currently in the ------(b)(4)----------. Clinical data from each of the five product generations were considered in support of product approval because their manufacturing processes are similar and their biochemical properties are comparable.

Octapharma has submitted data to support the following two of the six indications carried by FFP and PF24, which are listed in the current AABB Circular of Information and currently licensed in the US:

- Replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease, and in patients undergoing cardiac surgery or liver transplantation
- For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)

For reference, the other four indications for FFP and PF24 are:

- Patients undergoing massive transfusion who have clinically significant coagulation deficiencies
- Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect
- Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available
- Management of patients with rare specific plasma protein deficiencies, such as C1 esterase inhibitor, when recombinant products are unavailable

The dataset considered by FDA in support of safety and efficacy consisted of nine clinical studies conducted outside the US. The following limitations of the dataset were identified during the review process:

- There was no pivotal trial conducted to evaluate safety and efficacy
- Many of the studies were:
  - Small and uncontrolled
  - Underpowered to evaluate efficacy
  - Not hypothesis driven
  - Not focused on the indications for use
  - Primarily designed to compare product generations to one another

These limitations notwithstanding, most of the studies captured data from one or more of a number of predefined efficacy endpoints related to hemostasis, global measures of coagulation, and circulating levels of Protein S (PS) and Plasmin Inhibitor (PI; α-2-antiplasmin). These data provided substantial evidence to support the effectiveness and safe use of Octaplas™ in the indications for use.

Pharmacovigilance data submitted by Octapharma on all generations of its pooled plasma products dating back to the first approval in 1992 of Octaplas® in the EU provided further supportive data for safe use of the product. As stated above, these pharmacovigilance data encompass >2 million patient exposures. Although these pharmacovigilance data are derived from passive surveillance reporting and cannot definitively address safety issues, they are useful for generating safety questions that can be further evaluated with formal studies. The submitted pharmacovigilance data did not identify any new safety signals in comparison to the known safety profile from the clinical development program.

Chemistry, Manufacturing, and Controls critical issues discussed during BLA review:

Establishment of a final release specification that reflects clinical use, ensures clinical safety and product quality, and reflects manufacturing capability

Octapharma's proposed final product release specification was based on ---(b)(4)----------
------(b)(4)---------- ---
(b)(4)---------- provides for biochemistry testing and acceptance criteria listed in Table 2, which were adopted for final release of Octaplas™.

Table 2: Initial Product Release Biochemistry Testing

[(b)(4)]

Based on the intended use of the product as an alternative to FFP, the safety of the product with regard to adequate levels of Protein S and alpha–2–plasmin inhibitor, indication for treatment of patients with TTP and demonstrated manufacturing capability, Octapharma revised the final release specification to include tests and acceptance criteria as listed in Table 3, which was considered acceptable by the review committee. Protein S and alpha-2-plasmin inhibitor were --------(b)(4)----------, respectively to ≥0.4 IU/mL for both analytes.

Table 3: Revision of Final Product Specification

Biochemistry Test	Acceptance Criteria
Factor V	---(b)(4)---
Factor VIII	---(b)(4)---
Factor XI	---(b)(4)---
Fibrinogen	---(b)(4)---
Protein S	≥0.4 IU/mL
Alpha–2–Plasmin Inhibitor	≥0.4 IU/mL
Prothrombin	---(b)(4)---
Factor VII	---(b)(4)---
Factor X	--(b)(4)---
ADAMTS13	---(b)(4)--

Prion infectivity clearance

The manufacturing process for Octaplas™ incorporates an affinity chromatography step intended to remove prion infectivity. Prion clearance studies, however, did not demonstrate sufficient clearance of prion infectivity to support a claim (reduction factor of only 0.83 $\log_{10}$); therefore, a pathogen clearance claim for prions will not be permitted in the product label (full prescribing information – FPI).

3. Chemistry, Manufacturing and Controls (CMC)

a) Product Quality and Manufacturing Control

Octaplas™ is manufactured from pooled human plasma source material directly into final drug product within a (b)(4). time frame.

Control of plasma for further manufacture

FDA and Octapharma had several discussions concerning issues of plasma safety and biochemical quality as they related to source of material and time to freezing. Concurrence was reached between Octapharma and FDA that Octaplas™ may be manufactured from either Source Plasma or recovered plasma and that the quality agreement for plasma suppliers stipulate placement of each unit in a (b)(4) freezer within (b)(4) hr. of blood draw, freezing to an initial core temperature of $\leq$-25^{o}C followed by long term storage in a (b)(4) freezer.

FDA expressed concern regarding potential for increased viral transmission risk from Source Plasma starting material. The theoretically increased risk, however, is mitigated by: (1) Source Plasma blood establishment quality management in accordance with the International Quality Plasma Program (IQPP) standard of the Plasma Protein Therapeutics Association (PPTA) that governs donor qualification, quality assurance, donor deferral, education and training of personnel, and viral marker monitoring, (2) adventitious agents testing of individual units or mini-pools or manufacturing plasma pools, as appropriate, using FDA licensed kits including nucleic acid amplification testing for HAV, HBV, HCV, HIV, and HEV, (3) (b)(4) lots manufactured from Source Plasma that have been distributed since 2006 in Europe and Canada without report of seroconversion or transfusion transmitted disease and (4) the potential for a significantly decreased risk for Transfusion Related Acute Lung Injury (TRALI) that outweighs theoretically increased viral transmission risk from product manufactured with Source Plasma However, subjects were not prospectively monitored for TRALI in the clinical trials for FDA to grant this claim.

Product Attributes

Description and Composition

Octaplas™ is a frozen, sterile, pyrogen-free, solvent/detergent treated (1% tri-n-butyl phosphate/ 1% octoxynol), pooled human plasma product filled in 200 ml doses into 300 ml polyvinyl chloride plasma bags. It is manufactured from 630 to 1,520 single donor units from the same ABO blood group of Source Plasma and/or recovered plasma. Product composition is provided in Table 4.

Table 4: Product Composition

Ingredient	Amt. per 200 ml bag	Function	Standard
Human plasma containing expected spectrum of plasma proteins	9.0 – 14.0 g	Active	-(b)(4)-
Na-citrate·$2H_2O$	0.88 – 1.48 g	Anticoagulant	USP; Ph. Eur.
$NaH_2PO_4 \cdot 2H_2O$	0.06 – 0.24 g	Buffer	USP/NF; Ph. Eur.
Glycine	0.80 – 1.20 g	Osmolality regulator	USP/NF; Ph. Eur.

-----(b)(4)---------

[--(b)(4)--]

[(b)(4)]

Impurities

Octapharma has characterized the impurity profile for Octaplas™ as listed in Table 6.

Table 6: Octaplas™ Impurity Profile

Product Related Impurities	----------(b)(4)----------
Process-Related Impurites	• ---(b)(4)--- • Tri-n-butyl phosphate (TnBP) • Octoxynol (Triton X-100) • --(b)(4)-----

The impurity profile was determined for (b)(4) Octaplas™ conformance lots using routine finished product release testing. The impurity profiles were reproducible for all lots and values were within the specified limits.

Analytical characterization is considered to be comprehensive and complete and comparability has been demonstrated throughout pharmaceutical development. The biochemical profile indicates acceptable product quality.

Release Specification

Octaplas™ final product release specification is listed in Table 7. The release specification is considered adequate to confirm product quality and manufacturing consistency.

Table 7: Final Product Release Specification

Specification No. 013FPS952/05/US		
Test	**Method**	**Acceptance Criteria**
Characters		
Visual Control	---(b)(4)-----	Clear to slightly opalescent gelatinous particles
Identity		
---(b)(4)----------	----(b)(4)---------- ----	---(b)(4)---------- ---
---(b)(4)-----	---(b)(4)-------	---(b)(4)-------
Tests		
---(b)(4)------	---(b)(4)--------	---(b)(4)------
---(b)(4)------	---(b)(4)--------	----(b)(4)------
Protein	-----(b)(4)--------	45-70 mg/mL
---(b)(4)-----	---(b)(4)------	---(b)(4)----
---(b)(4)-----	---(b)(4)------	---(b)(4)----
---(b)(4)------	---(b)(4)-------	----(b)(4)----
--(b)(4)-----	---(b)(4)------	---(b)(4)----
---(b)(4)----	---(b)(4)------	---(b)(4)---
---(b)(4)-----	---(b)(4)----	---(b)(4)------
----(b)(4)-----	---(b)(4)-----	---(b)(4)-----
Sterility	---(b)(4)----	Sterile
Pyrogens	CFR §610.13	Free of pyrogens
Assays		
Factor II	-----(b)(4)-----	---(b)(4)---
Factor V	-----(b)(4)------	---(b)(4)----
Factor VII	---(b)(4)-----	---(b)(4)---
Factor VIII	---(b)(4)------	---(b)(4)---
Factor X	---(b)(4)------	---(b)(4)-----
Factor XI	----(b)(4)------	---(b)(4)---
Protein C	---(b)(4)-----	---(b)(4)--
Protein S	---(b)(4)-----	≥0.4 IU/mL
Plasmin inhibitor	--(b)(4)----	≥0.4 IU/mL

Specification No. 013FPS952/05/US		
Test	**Method**	**Acceptance Criteria**
(alpha-2-plasmin inhibitor)		
ADAMTS13	---(b)(4)-----	---(b)(4)---
---(b)(4)--------		
---(b)(4)-----		---(b)(4)----------
---(b)(4)---		---(b)(4)----------
---(b)(4)-----		
---(b)(4)----	---(b)(4)----	---(b)(4)-----
---(b)(4)---	---(b)(4)----	---(b)(4)-----
---(b)(4)---	---(b)(4)----	---(b)(4)----
---(b)(4)--	---(b)(4)--	---(b)(4)----
---(b)(4)---	---(b)(4)---	---(b)(4)----
---(b)(4)---	---(b)(4)----	---(b)(4)---
---(b)(4)---	---(b)(4)---	---(b)(4)----
---(b)(4)---	---(b)(4)---	---(b)(4)----

Octapharma requested an exemption from the General Safety Test. Their justification included an inability to properly perform the test due to the intrinsic irritant nature of plasma and adequate control of extraneous toxic contaminants through performance of the ----(b)(4)--------
Exemption from the General Safety Test will be granted.

Method of Manufacture and Packaging and Process Controls

Process Description

Octaplas™ is manufactured from 630 to 1,520 single donor units from the same ABO blood group of either Source Plasma and/or recovered plasma. During the manufacturing process, whole cells and cell fragments or debris are removed by filtration. Subsequently, the plasma pool is treated with a combination of the solvent, 1% tri-n-butyl-phosphate and the detergent, 1% octoxynol-9 (Triton X-100) to inactivate enveloped viruses. S/D reagents are removed by oil and solid phase extraction. After 0.2 µm sterile filtration, Octaplas™ is aseptically filled in 200 ml doses into plasma bags and rapidly deep frozen.

Control of Raw Materials and Reagents

Human Plasma Starting Material

The licensed product will be manufactured from either Source Plasma and/or recovered plasma placed in a (b)(4) freezer within (b)(4) hr. of blood draw.

Materials and Reagents of Non-animal/ Non-human origin

Chemical reagents, buffers and excipients are controlled to compendial standard. Column resins are controlled to internal quality standard. Representative certificates of analysis were submitted to the BLA. Control of raw materials and reagents was considered adequate.

Process Controls

The manufacturing process is controlled for quality and consistency at defined manufacturing steps through in-process quality control testing and adherence to established process parameters, as listed in Table 8. In response to discussions with the FDA, Octapharma has established in-

process control limits for critical process steps, S/D treatment and sterile filtration, which if exceeded would require notification to the FDA. Furthermore, limits for endotoxin ---(b)(4)---------(b)(4)--- procedures were revised to acceptable, quantitative values. Finally, Octapharma has implemented a validated nucleic acid amplification test for Hepatitis E virus (HEV) in the manufacturing plasma pool.

[(b)(4)]

Analytical Methods

Analytical methods have been validated to support quality control throughout manufacture and final product release and stability. The methods were well developed and are in use by Octapharma for control of other US- and/or EU-licensed plasma-derived products such as Factor VIII or Factor IX concentrates. Proper suitability controls were developed by Octapharma to ensure the validity of the methods.

Process Validation

Octapharma's approach to process validation was based on a stated objective for each manufacturing step, a risk assessment of each step as a basis for determining appropriate quality control tests, and acceptance criteria and documentation of results from conformance lot manufacture with reference to pre-determined acceptance criteria for operational parameters and quality control testing. The following conformance lots were manufactured as initial support of process validation (Table 9), which included lots manufactured at Vienna (OPG) or Stockholm

(OAB) facilities (see Facilities section below for facility addresses) from Source Plasma or 24 hr. recovered plasma from A, B or O blood types.

[(b)(4)]

(b)(4)-- lots were invalidated due to ---(b)(4)---------- Following implementation of corrective and preventive action, Octapharma manufactured –(b)(4)-additional conformance lots, ---(b)(4)----------, which complied with all pre-determined validation acceptance criteria. The intended commercial manufacturing process for Octaplas™ is considered to be validated.

Container/Closure System

Octaplas™ is aseptically filled into 300 mL polyvinyl chloride (PVC) plasma bags from (b)(4) suppliers. Filled and labeled bags are over-wrapped with ---(b)(4)----------film, vacuum sealed and subsequently frozen. The primary containers from the (b)(4) suppliers conform to (b)(4)------ standard and are considered suitable for their intended use. Container/closure integrity tests (CCIT) were performed successfully.

Stability

Stability data submitted to the BLA supported a shelf life of 24 months when stored at $\leq$-18^{o}C protected from light. The available stability data indicated no critical trends during the observed long-term storage period. After thawing, unopened product may be stored at 2 – 4°C for up to 12 hours or 20 – 25 °C for up to 3 hours.

Adventitious Agents Safety

Non-viral pathogen safety

Microbial safety is ensured through control of bioburden in source materials, adherence to current Good Manufacturing Practice, in-process quality control monitoring, validated sterile filtration and aseptic filling processes, and release and stability testing for sterility and pyrogens.

Viral safety

Source Plasma or recovered plasma used in the manufacture of Octaplas™ is supplied by US licensed blood establishments with acceptable current Good Manufacturing Practice compliance

status. Donor screening procedures for whole blood donations for recovered plasma comply with US regulation. Source Plasma establishments comply with the PPTA IQPP standard. Viral testing using FDA licensed test kits is performed for plasma donations with the paradigm presented in Table 10. Test results must be negative except for Parvovirus B19 NAT, which is limited in the plasma pool to 10.0 IU/µl.

Table 10: Plasma unit testing for blood borne viruses

Test	Test performed on		
	Each individual donation	---(b)(4)---	Plasma pool
Anti-HIV 1 and 2	X		X
HBsAg	X		X
Anti-HCV	X		
Syphilis	X[1]		
HCV NAT		(b)(4)	X
Parvo B19 NAT		(b)(4)	X
HIV-1 NAT		(b)(4)	X
HAV NAT		(b)(4)	X
HBV NAT		(b)(4)	X
HEV NAT			X

[1]test interval according to national regulations

The solvent/detergent treatment process has been validated in ---(b)(4)---------- experiments. Virus inactivation by S/D treatment was tested in two independent studies for HIV-1, Bovine Viral Diarrhea Virus (BVDV – a model virus for HCV), Pseudorabies Virus (PRV – a model virus for large, enveloped, DNA-containing viruses), and Sindbis Virus (SBV). The claimed log reduction factors for enveloped viruses are summarized in Table 11.

Table 11: Virus reduction factors for Solvent/Detergent Treatment

Manufacturing step	Virus reduction factor (log_{10})			
	HIV	PRV	SBV	BVDV
S/D treatment	≥ 6.18	≥ 5.03	≥ 5.31	≥ 5.12

HIV-1: Human Immunodeficiency Virus-1; PRV: Pseudorabies Virus; SBV: Sindbis Virus; BVDV: Bovine Viral Diarrhea Virus

Immune neutralization based on specified antibody levels and virus load control by NAT may contribute to the safety toward non-enveloped viruses such as Hepatitis A Virus (HAV). In addition, both this product and its predecessor, Octaplas®, have been marketed widely outside the US since 2009 and 1992, respectively, without reported virus transmission, with the exception of one case of reported B19 parvovirus transmission before implementation of the specified viral limit in the plasma pool of ≤10.0 IU/µL.

In order to reduce the risk of Hepatitis E Virus (HEV) transmission, Octapharma will maintain a specified level of antibody against HEV in the final product to be not less than 0.2 IU/mL. Moreover, Octapharma has implemented a validated HEV NAT to control virus level in the manufacturing plasma pool.

One targeted virus inactivation step was considered acceptable for this product because additional virus clearance processes may damage the quality of multiple plasma proteins in the product that are required for its safety and efficacy.

Prion clearance

Ligand chromatography was incorporated into the manufacturing process with the intent to remove prion protein (PrP^{Sc}) infectivity. The clearance studies submitted to the BLA were considered to be insufficient; therefore, prion infectivity removal capacity by the ligand chromatography step has not been established. The risk of transmitting Creutzfeldt-Jakob Disease (CJD) or variant Creutzfeldt-Jakob disease through products made from US sourced plasma is considered to be very small based on the absence of any reported case to date.

The adventitious agents safety profile for Octaplas™ is considered acceptable.

b) CBER Lot Release

Octaplas™ release to US market will be subject to CBER Lot Release. Product lots will be released by protocol review.

c) Facilities review/inspection

Pre-approval inspections of two Octapharma facilities were performed by the Center for Biologics Evaluation and Research.

1. Octapharma AB, (OAB)
   Elersvägen 40, SE - 112 75
   Stockholm, Sweden
   FEI: 3005559915

2. Octapharma Pharmazeutika Produktionsges.m.b.H, (OPG)
   Oberlaaer Strasse 235
   A-1100, Vienna, Austria
   FEI: 3002809097

The Stockholm site (OAB) was inspected from July 24-27 and July 30, 2012. The Vienna site (OPG) was inspected from August 1–3 and August 6-7, 2012.

-------(b)(4)----------

The primary facilities reviewer considers this submission approvable on the basis of the inspections conducted and the facilities information reviewed.

d) Environmental Assessment

A categorical exclusion under 21 CFR 25.31(c) was submitted to the file. The request is justified based on the review of the information provided.

4. Nonclinical Pharmacology/Toxicology

Octaplas™ appears to be safe for use in the clinical indications proposed by Octapharma. The safety of residual levels of tri-(n-butyl) phosphate (TNBP) and octyl phenyl ethoxylate (octoxynol, obtained as Triton X-100) detergents used to achieve viral inactivation was assessed by conducting: (1) acute, sub-chronic and developmental and reproductive toxicity (DART) studies in animals; (2) mutagenicity studies using (b)(4) and other *in vitro* assays; (3) clastogenicity studies using the ----(b)(4)---------- and (4) assays to assess hemolytic potential. The results from *in vivo* toxicology studies, including DART testing, indicated that the no observable adverse effect levels (NOAELs) for the TNBP plus Triton X-100 combination were far greater than the residual levels of both detergents present in the final Octaplas™ product. Results from ---(b)(4)---------- and the hemolysis assays suggested TNBP and Triton X-100 residuals at the expected human doses of ----(b)(4)-----(b)(4)-, respectively, are not mutagenic, clastogenic, teratogenic or hemolytic.

The toxicity and mutagenicity of ---(b)(4)----- that potentially leach from the ligand affinity column used in-process were also evaluated in a rat repeat-dose study and by the method of (b)(4), respectively. The risk associated with ---(b)(4)---- that potentially leach from the ligand column matrix was assessed using results generated during extraction and analytical studies. The extractions were performed by the matrix manufacturer with either ---(b)(4)---------- ----------(b)(4)-- at temperatures that exceeded those used in-process. The results from the analytical studies were used to assess risk to TTP patients repeatedly exposed to matrix leachates in Octaplas™. The results from the repeat-dose toxicity study in rats and the (b)(4) assay suggested that the levels of ---(b)(4)------ that potentially leach from the in-process ligand affinity column into the Octaplas™ product are safe in the approved indications for this BLA. The safety of leachates from the column resin itself, specifically ---(b)(4)-and its derivatives, has been qualified by data from published literature and from safety data in short-term clinical uses (e.g., in the management of preoperative or bleeding patients who require replacement of multiple coagulation factors).

Octaplas™ is approvable for licensure based on results from both a risk assessment and nonclinical toxicology studies conducted with the inactivating detergents and extractables/leachables from the components used in the manufacture of Octaplas™.

5. Clinical Pharmacology

No pharmacokinetic study was conducted to evaluate the pharmacokinetic comparability of Octaplas™ with FFP.

6. Clinical/ Statistical

a) Clinical Program

Seventeen studies were submitted by Octapharma in support of the Octaplas™ product approval for the proposed indications. One of the studies was a retrospective study that evaluated tolerability. In this study ~5000 units of Octaplas were transfused to 950 subjects and no adverse events (AEs) were reported. Since it is unlikely that there would be no AEs given the size of this study, it was excluded from consideration of the safety and efficacy of the product.

Two safety studies conducted in the postmarketing period evaluated anti-D immunization and non-enveloped viral protection. These two studies were excluded from consideration of the safety of the product because anti D immunization is not relevant to the indication sought and the second study only consisted of 5 patients.

Five of the remaining fourteen studies were literature reports without complete study reports and were considered only for evaluation of safety.

The remaining nine clinical studies were considered in support of safety and efficacy of Octaplas™ and can be placed into one of three different groupings. These groupings and the studies they are comprised of are as follows:

- Studies that include FFP as the comparator product:
  - LAS-1-02-D,
  - 19/PLAS/IV/91
  - LAS-1-03-UK

- Bridging studies that compare one generation of the product with another:
  - LAS-201
  - LAS-203
  - UNI-110
  - UNI-101

- Single arm studies:
  - 3PLASIV90
  - LAS-Study-1-D

Clinical data from each of the five product generations were considered in support of product approval because their manufacturing processes are similar and their biochemical properties are comparable.

There were limitations in the dataset identified related to study design. Many of the studies were small, uncontrolled, not hypothesis driven, and were focused on comparison of one product generation to another, rather than on the indications for use.

Nonetheless, most of the studies captured data from one or more of a number of predefined efficacy endpoints related to hemostasis, global measures of coagulation, and circulating levels of PS and PI which provided substantial evidence to support the effectiveness and safe use of OctaplasLG/Octaplas™ in the indications for use.

Bioresearch Monitoring

In consultation with the medical reviewer, two sites were selected for Bioresearch Monitoring (BIMO) inspections by the Division of Inspections and Surveillance (DIS). The first site was selected because the US IND was conducted at this site and the second site was selected because it had the largest number of subjects enrolled in a study.

- Study LAS-203 was conducted under US IND by a clinical investigator in Vienna, Austria. BIMO inspection concluded that the clinical site conducting the study did not reveal problems that impact the data submitted in the application.

- Study LAS-201 was an observational study and access to source documents was not permitted in accordance with European and German law (since obtaining informed consent was not required). During the inspection the FDA investigator was informed that study physicians reviewed the records and retrospectively selected subjects for enrollment into the study. Since the subjects' outcome was known prior to enrollment, this leads to a potential for selection bias.

  Further, the study investigators did not enroll all subjects eligible for the study strictly by the study inclusion criteria. Some subjects were selected for enrollment based on the individual criteria of the study investigators in addition to the study required criteria.

  Due to these findings the efficacy outcomes from this study were non-interpretable.

Efficacy Analysis

Comparator Studies with FFP

There were three studies that compared Octapharma's solvent/detergent treated plasma with FFP (N = 188). These studies were all prospective and unblinded, and only one was randomized. None of the studies were hypothesis driven and only one study had a non-laboratory based predefined clinical efficacy endpoint (subjective assessment of hemostasis). The table below summarizes the three studies:

Table 12: FFP Comparator Studies

Study (Year)	Design	Products	Clinical Setting	Total Patients
LAS-1-02-D (1998)	Prospective, open-label, single-center	Octaplas (G-2a) and FFP	ICU post-open heart surgery	67
19/PLAS/IV/91 (1992)	Prospective, open-label, single-center	Octaplas (G-1), FFP and no plasma	Open heart surgery	66
LAS-1-03-UK (1995)	Prospective, open-label,	Octaplas (G-2a) and FFP	Liver disease, Liver transplantation,	55

Study (Year)	Design	Products	Clinical Setting	Total Patients
	randomized, multi-center		TTP requiring plasma exchange or infusion	

LAS-1-02-D (Octaplas G-2a)

LAS-1-02-D was a prospective, non-randomized open-label study conducted at a single center, in post-operative open heart surgery patients located in the surgical intensive care unit. These patients were in need of plasma transfusion for acute bleeding or for the risk of bleeding. There were a total of 67 patients, 36 who received Octaplas (600 mL) and 31 who received FFP (600 mL).

Predefined efficacy endpoints included the difference between baseline and post-infusion coagulation laboratory parameters at 30 and 60 minutes and a subjective impression of hemostasis, rated as good, satisfactory, or not satisfactory by the investigator.

The reported efficacy results showed similar levels at 30 and 60 minutes for post-infusion coagulation laboratory parameters for both products, with the exception of Plasmin Inhibitor levels which were lower in the Octaplas group. These results are shown in the table below.

Table 13: Absolute Mean Value Difference from Baseline at 30 and 60 minutes

		Octaplas (N = 36)	FFP (N = 31)
PT (%)*	30 min minus Baseline	6.0	5.2
	60 min minus Baseline	6.9	5.1
aPTT (sec)	30 min minus Baseline	-4.5	-7.8
	60 min minus Baseline	-5.9	-8.7
Total Protein S (U/dL)	30 min minus Baseline	-0.9	4.9
	60 min minus Baseline	-1.2	5.4
Free Protein S (U/dL)	30 min minus Baseline	5.2	3.9
	60 min minus Baseline	5.9	3.8
Plasmin Inhibitor (U/dL)	30 min minus Baseline	-9.5	-3.6
	60 min minus Baseline	-8.6	-1.7

Adapted from Octapharma Final Study Report LAS-1-02-D, page 20 and 21 of 32
**Expressed as percentage of normal from 50 healthy individuals*

The rate of hemostasis reported as "good or satisfactory" was 72% for Octaplas and 77% for FFP.

There were no adverse drug reactions reported, and no thrombotic complications were observed during and after the infusion of the products. Fourteen patients died during this study, four in the Octaplas treatment group and ten in the FFP group. In all cases death was judged to be unrelated to the treatment. No differences between the treatment groups with respect to vital signs were observed.

Plasmin inhibitor levels were lower in patients receiving Octaplas; however, this finding was of no clinical significance.

19-PLAS-IV-91 (Octaplas G-1)

19-PLAS-IV-91 was a prospective, non-randomized open-label study conducted at a single center in patients undergoing open heart surgery. There were a total of 66 patients: 20 who received Octaplas [mean 3.5 units (range 1 – 17)]; 26 who did not receive any plasma; and an historical control group of 20 who received FFP [mean 4 units (range 2 – 16)].

There were no predefined efficacy endpoints. The results of clinical examinations were reported as shown in the table below:

Table 14: Post-operative Course and Complications

Parameter	**Octaplas (N = 20)**	**FFP (N = 20)**	**No plasma (N = 26)**
Reoperation for bleeding (n)	4	4	2
Respirator time (h)	38	57	6
Post-operative bleeding (mL)	1139	993	684
Need for circulatory support (n)	1	1	0
Post-operative hospital stay (days)	6	6	5

Adapted from Octapharma Final Study Report 19-PLAS-IV-91, page 20 of 26

One patient in the Octaplas group experienced a transient increase in temperature. No abnormal liver function tests or seroconversions were observed in 16 patients who were followed for 6 months after receiving Octaplas.

LAS-1-03-UK (Octaplas G-2a)

LAS-1-03-UK was a prospective, randomized, open-label, multi-center study in patients with coagulopathy due to liver disease (LD) or liver transplant (LT), and in patients with TTP. There were a total of 52 patients who completed the study; 3 did not. The number of patients in each treatment group and their exposure to plasma product is shown below.

Table 15: Number of Patients per Treatment Group and Exposure to Plasma Product

	Octaplas	**FFP**
LD N = 24	N = 13 median dose 12 (range 11 -15) mL/kg	N = 11 median dose 13 (range 11 -17) mL/kg
LT N = 25	N = 12 median dose 44 (range 25 -104) mL/kg	N = 13 median dose 44 (range 7 -71) mL/kg
TTP N = 3	This portion of the study was not randomized. All 3 patients received Octaplas, 3 liters daily until stable remission was achieved. Treatment periods for the 3 patients were 9 days, 28 days and 35 days.	

Predefined efficacy endpoints in the LD/LT groups were global measures of coagulation, and correction of specific coagulation factors as well as Protein C. In the TTP group predefined efficacy endpoints were platelet count and laboratory values.

In the LD/LT groups, the initial dose was 400 mL followed by further dosing as clinically indicated for up to 24 hours. In the TTP group the dose was dependent upon whether plasma infusion or exchange was performed and how many plasma exchanges were carried out. The maximum was up to three liters per day for a total of 14 days.

The table below shows global measures of coagulation following 400 mL of plasma in the LD/LT groups. The degree of correction of the global measures of coagulation was similar for both products within each clinical setting (i.e., LD or LT).

Table 16: Effects of FFP and Octaplas on INR/aPTT after 400 mL of Plasma

		FFP Baseline	**Octaplas Baseline**	**FFP After 400 mL Plasma**	**Octaplas After 400 mL Plasma**
INR median (range)	LD	2.0 (1.4-3.1)	3.0 (1.5-5.8)	1.8 (1.4-2.4)	2.3 (1.5-3.3)
	LT	1.5 (0.9-3.9)	1.5 (1.0-3.9)	1.6 (1.0-3.5)	1.6 (1.0-3.2)
aPTT prolongation* (sec) median (range)	LD	23 (10-69)	27 (7- >100)	20 (9-49)	27 (7-60)
	LT	13 (-12-90)	15 (-3-63)	14 (-3-74)	22 (-2-57)

Source: Williamson et al. 1999

**aPTT values are expressed as the difference between the clotting times (in sec) of the test plasma and the laboratory control*

The degree of correction of coagulation factors measured, including Protein C, was also similar for the two products within each clinical setting.

The three TTP patients were reported to have attained platelet counts > 50 x 10^9/L by day 10.

There were two acute drug reactions in one LD patient (nausea, pruritis) who received Octaplas. There were two reports of hemorrhage, both in LT patients, one who received Octaplas and one who received FFP. No thrombotic events were reported.

Conclusions for FFP Comparator Studies

The conclusions for the FFP comparator studies are as follows:

- There were 188 patients studied in three trials that compared safety and efficacy of Octaplas to FFP in clinical conditions associated with coagulopathy

- Three acute drug reactions were reported in two subjects
  - Transient fever reaction
  - Nausea
  - Pruritis

- The efficacy and safety outcomes were similar between prior generations of Octaplas products and FFP in various clinical conditions where replacement of multiple coagulation factors were needed,

Bridging Studies Comparing One Generation Product to Another

There were four studies that compared different generations of Octapharma's biochemically similar solvent/detergent treated plasma products with one another. Two of the four studies were conducted in a patient population, and the other two studies were conducted in healthy volunteers. One of the studies was an observational study from which efficacy conclusions were unable to be drawn due to the retrospective nature of the study and to potential selection bias (see LAS-201under Bioresearch Monitoring above). The table below summarizes the four studies:

Table 17: Bridging Studies Between Different Product Generations

Study (year)	Design	Products	Clinical Setting	Total Patients
UNI-101 (1999)	Prospective, randomized, controlled, blinded	Octaplas (G-2a), Uniplas and no plasma	Elective open heart surgery	84
LAS-201 (2008)	Observational, open-label, multi-center, sequential cohort	Octaplas (G-2a) and OctaplasLG	Any clinical condition with a need for plasma	125
LAS-203 (2009)	Prospective, randomized, open-label, controlled, cross-over, single center	Octaplas (G-2a) and OctaplasLG	Healthy volunteers	60
UNI-110 (2009)	Prospective, randomized, double-blind, controlled, cross-over, single center	OctaplasLG and UniplasLG	Healthy volunteers	30

UNI-101 (Octaplas G-2a and Uniplas G-3a)

UNI-101 was a prospective, randomized, blinded, single center study designed to compare the safety and tolerability of Uniplas with generation 2a Octaplas in patients undergoing elective open heart surgery. There were a total of 84 patients, 36 who received Uniplas (divided into groups by blood group, A, B, and AB [n = 25] and O [n = 11]), and 19 who received Octaplas. There were also 29 patients who received no plasma (eligible patients who gave informed consent but did not require any peri-operative plasma transfusion) included in the study.

The dosage of plasma product was based upon the individual clinical situation (coagulopathy due to blood loss and/or dilution, and for warfarin reversal) and adjusted according to the needs of each patient. Transfusions could be given for the purpose of study evaluation intraoperatively and up to post-operative Day 2. The minimum dose given in the active treatment groups was one transfusion with one bag (bag = 200 mL) for either Uniplas (n = 10) or Octaplas (n = 1). The maximum dose given during one transfusion episode was seven bags of Uniplas. The maximum total dose given to one individual patient during the study was 23 bags of Uniplas.

Predefined efficacy endpoints were the global measures of coagulation, aPTT and activated clotting time (ACT), reported as change from baseline at the conclusion of surgery, at post-operative Day 1 and post-operative Day 2.

Measured values of aPTT and ACT were available for 73 subjects. The laboratory values of aPTT and ACT were comparable in the three active treatment groups: aPTT values returned to baseline by post-operative Day 1 and ACT values were slightly below baseline at the conclusion of surgery.

There were no acute drug reactions reported. Post-operative adverse events (e.g. atrial flutter, decreased cardiac output etc.) were evenly distributed in the four groups (no bleeding complications or need for reoperation was reported for the no plasma group) and appeared to be related to the underlying cardiac condition rather than causally related to either treatment. There were two reports of hemorrhage in the group who received Uniplas and three in the group who received Octaplas.

LAS-201 (Octaplas G-2a and OctaplasLG G-2b)

LAS-201 a non-interventional, sequential cohort, observational, open-label, prospective, multi-center study in patients who needed of plasma for any clinical condition. The observation period per patient depended on the indication to be treated, but generally was expected to be a period of one to two days. A total of 125 patients were enrolled in the study. Initially, all patients enrolled in the study received Octaplas, and when OctaplasLG was marketed an additional 60 patients were enrolled and received OctaplasLG.

The efficacy of the treatment with Octaplas or OctaplasLG was judged by the investigator based on clinical and laboratory parameters relevant for the indication. However, study subjects were not enrolled until after the study physicians knew whether the treatment was successful and whether any adverse reactions had occurred, leading to potential enrollment bias. Therefore, efficacy outcomes were unable to be interpreted.

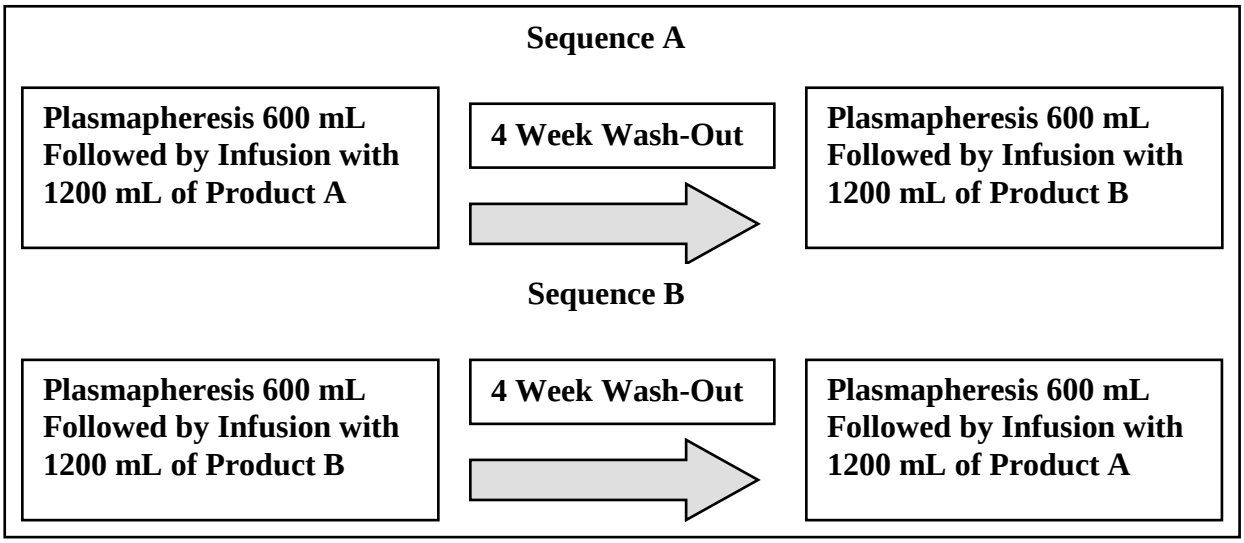
There was one serious adverse event reported in the OctaplasLG group, a case of severe hypotension that required treatment with a cardiac stimulant. The patient recovered after 20 minutes.

LAS-203 (Octaplas G-2a and OctaplasLG G-2b) and UNI-110 (OctaplasLG G-2b and UniplasLG G-3b)

LAS-203 (N = 60) and UNI-110 (N = 30) were both prospective, randomized, cross-over design studies in healthy volunteers. The objective of the studies was to compare the safety and impact on laboratory parameters of one generation product to another.

Prior to plasmapheresis of 600 mL of plasma, each healthy volunteer was randomly assigned to one of two possible treatment sequences (A or B): Sequence A subjects received Octaplas in LAS-203 and UniplasLG in UNI-110 followed by OctaplasLG in LAS-203 and OctaplasLG in UNI-110. Sequence B subjects received treatment in the opposite order. In each case, the volume of plasma product infused was 1200 mL. Figure 1 below diagrams the design of the study.

Figure 1: Two Possible Treatment Sequences for LAS-203 and UNI-110



In UNI-110 the change in the measured coagulation parameters (aPTT, fibrinogen, FII, FV, FVII, FVIII, FIX, FX, FXI, PS and PI) over time (baseline, immediately following plasmapheresis and after infusion with SDP product) were compared between the two products. The results showed that mean values of coagulation parameters were within the normal range and variations in their levels were similar between treatment groups.

Subjects were not pre-medicated with either anti-allergic or antipyretic medications prior to plasma product infusion. There were 92 acute drug reactions that occurred in 27 subjects. The most frequent adverse drug reactions were paresthesia, headache and urticaria, which occurred at similar rates in the two treatment arms as seen in the table below.

Table 18: Most Frequent Acute Drug Reactions

Acute Drug Reaction	OctaplasLG (N = 30)	UniplasLG (N = 30)
Paresthesia # (%)	6 (20)	7 (23)
Headache # (%)	7 (23)	10 (33)
Urticaria # (%)	6 (20)	6 (20)

In LAS-203 the following parameters were assessed:

- Coagulation factors
- Hemostatic parameters (aPTT, PT and protein C)
- Hematology parameters (RBC count, WBC count, platelets, hematocrit, hemoglobin, PI, and PS)
- Clinical chemistry

The primary analysis was to demonstrate equivalence for recoveries of coagulation factors using a 10% margin.

For each coagulation parameter the recoveries were analyzed by performing two one-sided paired t-tests of the hypothesis

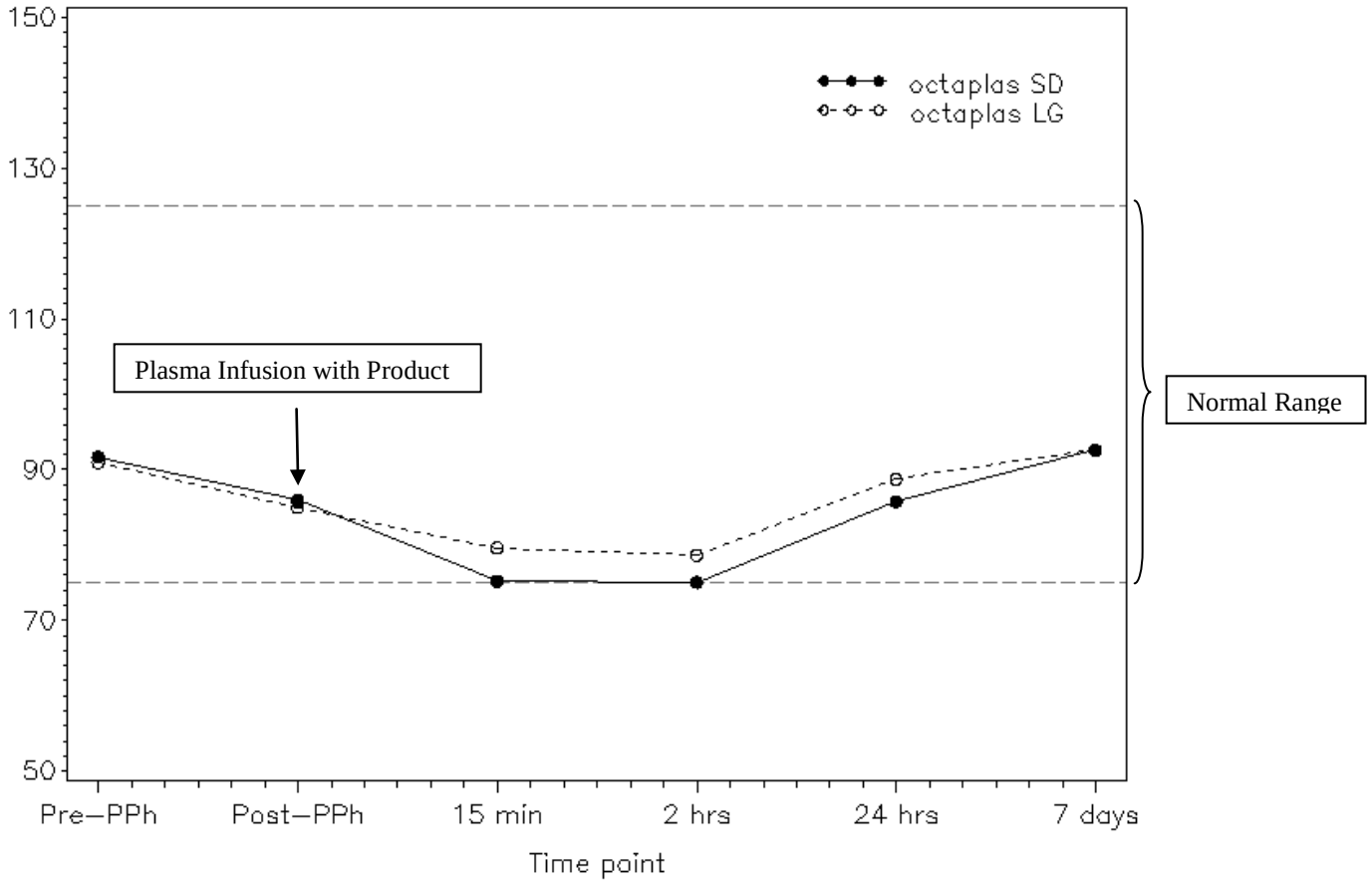
H_0: |mean(Recovery(OctaplasLG)) - mean(Recovery(Octaplas))| > 10.0 %

vs.

H_1: |mean(Recovery(OctaplasLG)) - mean(Recovery(Octaplas))| ≤ 10.0%.

All coagulation and hemostatic parameters met the equivalence criterion. To verify the assumption of improvement of PI concentrations, a test for superiority was conducted. Statistically significant differences between treatments were found at 15 minutes (P=0.0012) and two hours (P=0.0190) post-transfusion for the per protocol population. Increased levels of PI post-infusion of OctaplasLG, as compared to Octaplas may be attributable to the increased levels of PI in the OctaplasLG product.

Figure 2: Time Courses of Plasmin Inhibitor Concentration



Source: Report Clinical Study LAS-203; December 2011, Page 62

Subjects were not pre-medicated with either anti-allergic or antipyretic medications prior to plasma product infusion. In total, 158 adverse drug reactions were reported in 60 subjects (77 in OctaplasLG and 81 in Octaplas). The adverse drug reactions (paresthesia, headache and urticaria) reported in both groups were mild to moderate and occurred at similar rates as shown in the table below. There was one serious adverse event, anaphylactic shock. The patient recovered with appropriate management.

Table 19: Most Frequent Acute Drug Reactions

Acute Drug Reaction	Octaplas (N = 60)	OctaplasLG (N =60)
Paresthesia # (%)	8 (13)	14 (23)
Headache # (%)	11 (18)	12 (20)
Urticaria # (%)	12 (20)	13 (21)

Conclusions for Bridging Studies

The conclusions for the bridging studies are as follows:

- There were four studies that compared OctaplasLG to Octaplas or UniplasLG
- A total of 299 subjects were studied

- There were 90 healthy volunteers (all exposed to OctaplasLG)
- There were 84 heart surgery patients
- There were 125 patients needing plasma for any condition

- The observed comparability in laboratory values supports comparability between product generations resultant of their similar manufacturing and biochemical profiles except for Plasmin Inhibitor values in Study LAS-203

- There was no imbalance in acute drug reactions between the three products

- Acute drug reactions reported in two healthy volunteer studies, most frequent for OctaplasLG include:
  - Paresthesia 22%
  - Headache 21%
  - Urticaria 18%

- Two serious adverse events reported with OctaplasLG
  - Severe hypotension in observational study
  - Anaphylactic shock in LAS-203

Single Arm Studies

There were two single arm studies. These studies were conducted in 1990 and 1992, utilizing a formulation of the product that is no longer marketed.

Table 20: Single Arm Studies

Study (year)	Design	Products	Clinical Setting	Total Patients
3PLASIV90 (1990)	Prospective, open-label	Octaplas (G-1)	Hereditary or acquired coagulation factor deficiency	11
LAS-Study 1-D (1992)	Prospective, open-label	Octaplas (G-1)	ICU patients with DIC	30

3PLASIV90 (Octaplas G-1)

3PLASIV90 was a prospective, non-controlled, open-label study in patients with hereditary or acquired coagulation factor deficiencies. The objective of the study was to assess the effects of Octaplas on coagulation parameters in subjects with a hereditary (FVII, X or XI deficiency, n = 8) or acquired (due to liver disease, n = 3) coagulation factor deficiency. There were a total of 11 patients evaluated.

Predefined efficacy endpoints were recovery of coagulation factors in hereditary coagulation factor deficiency and the investigators clinical impression of overall effectiveness for stopping or preventing bleeding.

The results demonstrated:

- Effective replacement of deficient coagulation factors as shown by expected recovery levels in eight patients with hereditary coagulation factor deficiency

- Hemostasis was achieved in two patients with bleeding (hemarthrosis and menorrhagia)

- Prophylaxis was rated as "good" in eight patients undergoing invasive procedures

Two patients experienced a total of three adverse reactions, consisting of an anaphylactoid reaction, and urticaria with pruritis. These adverse reactions resolved with anti-histamine therapy and both patients recovered.

LAS-Study 1-D (Octaplas G-1)

LAS-Study 1-D was a prospective, non-controlled, open-label study in 30 patients in the intensive care unit with coagulopathy due to blood loss, dilution or disseminated intravascular coagulation. Thirty patients were evaluated after a single 200 mL infusion of Octaplas.

Predefined efficacy endpoints were improvement in coagulation parameters including PT, aPTT, Fibrinogen, Antithrombin III and platelet count. Improvement in PT, aPTT Fibrinogen and Antithrombin III is shown in the table below.

Table 21: Results of Coagulation Parameters after a Single 200 mL Infusion of Octaplas (N = 30)

Parameter	Normal Laboratory Reference Range Used	Before Infusion (mean ±SD)	After Infusion (mean ±SD)
PT (%)	70 – 100	62 ±16	67 ±17
aPTT (sec)	28 - 41	48 ±18	43 ±13
Fibrinogen (g/L)	1.45 – 3.85	3.09 ±1.46	3.55 ±1.54
Antithrombin III (%)	80 - 100	54 ±16	64±18
Platelet count (#/nl)	140 - 400	160 ±85	160 ±70

Adapted from Octapharma Final Study Report LAS-Study 1-D, page 23 of 26

Additionally, a hemostatic effect was reported by the investigators in 16 of 22 patients who had manifest bleeding prior to infusion. There were no adverse drug reactions reported.

The conclusions for the single arm studies are:

- Functional levels of coagulation factors were recovered in eight patients with hereditary coagulation factor deficiency

- Hemostasis was achieved in 18/24 bleeding patients (total for both studies)

- Prophylaxis for hemostasis was rated as effective by the investigator in 8/8 patients undergoing an invasive procedure

- Two patients exhibited a total of three acute drug reactions
  - Anaphylactoid reaction, and urticaria with pruritis

Overall Efficacy Conclusions

The overall efficacy conclusions are as follows:

- When evaluated, global measures of coagulation were either corrected or trended towards correction
- Deficient coagulation factors were replaced to expected levels
- Infusion with OctaplasLG led to higher circulating plasma levels of Plasmin Inhibitor when compared with Octaplas
- Hemostasis or prophylaxis for bleeding prior to invasive procedure was reported as successful in the majority of cases for which it was evaluated
- Bridging studies support comparability among product generations

b) Pediatrics

The application triggered PREA as a new indication. Octapharma requested a pediatric deferral for all age groups. The pediatric assessment was presented to the Pediatric Review Committee (PeRC) on September 12, 2012. The PeRC agreed with the Division to grant a full deferral because the product is ready for approval in adults; however, pediatric studies encompassing all age groups (< 16 years) will need to be completed in the post-marketing period for both indications for use.

Octapharma has agreed to conduct the following postmarketing required pediatric studies in ages <16 years old:

- An open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients who require multiple plasma coagulation factors to be completed by February 2016
- A non-interventional, open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients who require therapeutic plasma exchange to be completed by March 2017

7. Safety

The overall safety profile of Octaplas™ is acceptable. The majority of the reported adverse drug reactions were mild to moderate and seen in healthy volunteers. The most common (≥ 1%) adverse drug reactions reported were paresthesia, headache, urticaria, nausea, and pruritis. The healthy volunteers were not pre-medicated with either anti-allergic or antipyretic medications prior to plasma product infusion. The table below shows the pooled safety database for Octaplas (G-1 and 2a) and Octaplas™.

Table 22: Pooled Safety Database for OctaplasLG and Octaplas from Nine Clinical Studies Considered in Support of Safety and Efficacy

Adverse Event	OctaplasLG (N = 120) # (%)	Octaplas (G-1, 2a) (N = 239) # (%)
Anaphylactoid reaction	0	1 (0.4%)
Pruritis	2 (1%)	3 (1%)
Urticaria	19 (15%)	13 (5%)
Fever	0	1 (0.4%)
Nausea	4 (3%)	2 (0.8%)
Headache	19 (15%)	11 (4%)
Paresthesia	21 (17%)	8 (3%)
Hyperfibrinolysis	0	0
TRALI	0	0

There were two serious adverse events reported. One was a case of severe hypotension and the other was anaphylactic shock. Both patients recovered with appropriate management. There were no deaths due to transfusion of any of the generations of Octapharma's solvent detergent plasma product reported in the clinical trials.

One of the major risks of treatment with blood components, including plasma, is transmission of infectious disease agents. This risk has been largely reduced by donor screening questionnaires, and screening of donors by serology and NAT.

Octaplas™ is a product pooled from up to 1520 plasma donations. Risk of patient exposure to a large number of donors is offset by solvent/detergent treatment to inactivate enveloped viruses. Risk from non-enveloped viruses in Octaplas™ is reduced by limiting viral load using NAT, and by minimal titer specifications for HAV and B19 neutralizing antibodies. To date, there have been no documented cases of infection with HBV, HCV or HIV associated with the use of Octaplas® or Octaplas™.

One case of B19 transmission (NAT positive after 9 months) has been reported with the use of Octaplas manufactured prior to the implementation of Parvovirus B19 DNA limits (i.e., B19 not to exceed more than 10.0 IU/μL in the manufacturing plasma pool). No clinical symptoms were observed or reported in this patient. There have been no cases of HAV transmission reported.

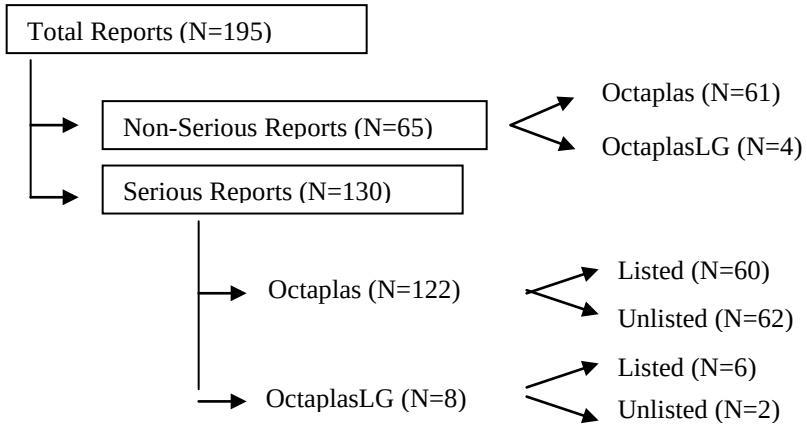
Despite the very low presumptive prevalence of vCJD infection in US donors, the pooling of plasma for the manufacture of OctaplasLG may increase the risk of vCJD due to the absence of significant prion clearance in manufacturing (i.e. estimated clearance of vCJD agent by the ligand gel column of only 0.83 $\log_{10}$). Nevertheless, the extensive experience showing apparent reduction in risk of TRALI (see below) and related deaths with Octaplas indicates that the demonstrated benefit of TRALI reduction would exceed the potential added vCJD risk.

Pharmacovigilance Data

FDA reviewed all submitted pharmacovigilance data from outside the United States for Octaplas®G-1 and G-2a and OctaplasLG®. The results are summarized here.

- Over 21 years of postmarketing surveillance data are available for Octaplas®G-1 and G-2a. Since the initial octaplas® approval on 27 October 1989, Octaplas®G-1 and G-2a have been approved in 28 countries worldwide, totaling 7 million units (200mL bags) sold and an estimated 2.3 million patients exposed.
- Over 2 years of postmarketing surveillance data are available for OctaplasLG® (G-2b). Since the first approval in June 2009, OctaplasLG® has been approved in ten countries, totaling ---(b)(4)- units (200mL bags) sold and an estimated 41,500 patients exposed.
- From 27 October 1989 to 31 August 2011, a total of 195 adverse event reports were received worldwide describing 407 types of events. Of these, 144 (74%) were spontaneous reports from healthcare providers, 36 (18%) from regulatory authorities, 13 (6%) from the medical literature, and two (1%) from clinical studies.

Figure 3: Distribution of 195 Reports between Octaplas and OctaplasLG



** Listed / unlisted refers to whether the adverse event appears in the package label and was determined by Octapharma.*

Serious Reports

Table 23 summarizes all serious reports on a patient basis. Each report was consolidated under the most serious and related condition, in terms of causality, to the administration of one of the generations of Octaplas products as determined by Octapharma pharmacovigilance reviewers. All adverse event reports were represented only once, except one case that was listed twice as both a suspected transmission and hypersensitivity reaction.

Table 23: Worldwide Summary of Serious Adverse Events for Octaplas®G-1 and G-2a and OctaplasLG — October 1989 to August 2011 (N=130)†

	Report Category	No. Unrelated Cases*		No. Related Cases**	
		Octaplas	OctaplasLG	Octaplas	OctaplasLG
1	Hypersensitivity reactions including	2	0	42	5

	Report Category	No. Unrelated Cases*		No. Related Cases**	
	anaphylactic and allergic reactions				
2	Respiratory disorder (not elsewhere classified)	2	0	10	2
3	Circulatory overload	1	0	5	0
4	Seroconversions (passive transfer of antibodies)	0	0	5	0
5	Thromboembolism	0	0	4	0
6	Other (alkalosis, medication error, etc.)	2	0	2	1
7	Cardiac disorder (not elsewhere classified)	4	0	2	0
8	Isolated fever and chills	0	0	2	0
9	Citrate toxicity	0	0	1	0
10	Hyperfibrinolysis	0	0	1	0
11	TRALI	0	0	0	0
12	Hemolytic transfusion reaction	0	0	0	0
13	Suspected transmission of infectious agents	38	0	0	0
	TOTAL	49	0	74	8

** Classified as not related, unlikely, unclassifiable*
*** Classified as possible or probable*
† All adverse event reports were represented only once except one case was listed twice as both a suspected transmission and hypersensitivity reaction.

The three most frequent serious adverse events reported after Octaplas® and Octaplas™ were hypersensitivity reactions, respiratory disorders, and circulatory overload. Reports of thromboembolism and hyperfibrinolysis, historically a source of concern with solvent/detergent-treated plasma products, were also detected.

Deaths

Reports of deaths occurring in association with the administration of the Octaplas products have been few and most have been judged by the sponsor to be unrelated to the product. Table 24 summarizes those death reports where the fatality was judged by the sponsor to be possibly related to the infusion of the Octaplas product.

Table 24: Summary of Deaths Judged by Octapharma to be Possibly Related to Octaplas®G-1 or G-2a or OctaplasLG

Manufacturer Report Number	Adverse Event (MedDRA preferred term)
LAS-011-02-IRL	fibrinolysis, hemorrhage, coagulopathy
LAS-015-02-IRL	therapeutic response decreased, cardiac arrest, fibrinolysis
LAS-006-07-DE	acute pulmonary edema
LAS-002-06-IRL	hypotension, cardiac arrest
LAS-024-10-LU	pulmonary edema, transfusion related circulatory overload

In summary, compared to the known safety profile from the clinical development program, no new safety signals have been identified after >2.3 million patients have been exposed to all Octaplas formulations. Passive surveillance data, however, serves as a safety net after licensure for rare or unusual events and should be interpreted as hypothesis generating. Although passive surveillance cannot determine the true rates of adverse events, the international post-licensure data provided by Octapharma are reassuring.

Three specific safety concerns with plasma in general (TRALI) and with solvent/detergent treated plasma are discussed below:

1. Low Protein S levels and risk of Thromboembolism

In 1998, FDA licensed PLAS+SD, a solvent/detergent treated, pooled human plasma, manufactured by V.I. Technologies Inc, Melville, NY. This product is no longer available on the US market. It was associated with thromboembolic events (TE) events especially in liver transplantation and liver disease. The TE events were believed to be due to low levels of PS in PLAS+SD. Solheim et al.[1] have reported a mean PS level of 64 U/100 mL (range 55-71) in Octaplas® G-2a vs. 24 U/100 mL (range 14-37) in PLAS+SD, the normal reference range being 56-168 U/100 mL[2]. Differences in PS between products may be attributable to manufacturing differences. The level of PS in Octaplas™ is higher than the levels detected in Octaplas®G-2a (Table 5).

In 2003, Yarranton et al.[3] published a retrospective review of the occurrence of venous thromboembolism (VTE) in 68 consecutive patients with TTP (25 male, 43 female) undergoing plasma exchange (PEX). Eight documented VTE events were noted in seven patients (5 deep venous thromboses (DVTs), 1 pulmonary embolus (PE), 1 PE + pulmonary arterial thrombosis and 1 PE + DVT). VTE occurred at a mean of 53 days following the first PEX. Octaplas® G-2a was the last plasma to be used in PEX prior to the VTE in 7/8 events. Other replacement fluids used were FFP and cryosupernatant (CSP). All the DVTs were associated with central venous catheters. The one pulmonary artery thrombosis was related to a Swan–Ganz catheter in the pulmonary artery. Other acquired precipitating factors for VTE for the eight events included pregnancy (n=1), immobility (n=8), and obesity (n=3).

PS levels were not routinely measured during PEX prior to the VTE event; however, archived plasma samples were available for one patient. Mean PS levels were lower in this patient following Octaplas® compared with CSP; however, for both treatments the mean levels remained within the normal reference range.

Yarranton et al. reported a background rate of 3% for VTE in this patient population[4]. The rate in their study was 12%. There have been no further reports of VTE associated with Octaplas® in the clinical studies, literature references, or post-marketing reports.

The risk of TE is still a concern especially where large volumes are needed, but this may be mitigated in OctaplasLG which has higher levels of PS (within the lower limit of the reference range, Table 5)

2. Low PI (α_2 antiplasmin) levels and risk of bleeding (hyperfibrinolysis)

Hyperfibrinolysis may occur during orthotopic liver transplantation (OLT) and has been associated with excessive bleeding during the procedure. Low levels of PI in Octaplas® have been implicated in an increased incidence of hyperfibrinolysis seen in patients undergoing OLT, as reported by de Jonge et al.[5] De Jonge and his colleagues reported the experience of 41 patients treated with FFP or Octaplas® (N= 21 FFP, N=20 Octaplas®). Hyperfibrinolysis was seen in 6/21 (29%) of the patients who received FFP and 15/20 (75%) of the patients who received Octaplas®.

Intra-operative plasma samples from both patient groups were analyzed and markers of fibrinolysis (D-dimer and fibrin degradation products [FDP]) were higher in the Octaplas® group than in the FFP group. This is in contrast to levels at the time of anesthesia onset, when no difference in PI levels was detected between the two groups. PI levels in the FFP treated group decreased from 0.76 IU/mL to a low of 0.58 IU/mL by procedure end. The PI level in the Octaplas® treated group began at 0.64 IU/mL, dropped to a low of 0.27 IU/mL by the time of reperfusion, and was at a level of 0.40 IU/mL by procedure end. Analysis of the Octaplas® lots used in these patients showed levels of PI to be 0.28 ±0.02 IU/mL (normal, 0.95 – 1.20 IU/mL)[2]. The PI levels in these lots appear to be lower than those measured in OctaplasLG (Table 5).

Two cases of hyperfibrinolysis were reported from Ireland.[6] The authors reported that shortly after the change from FFP to Octaplas® (derived from US donor plasma), 2 of 22 patients died intraoperatively during liver transplantation with severe coagulopathy and excessive bleeding. Both patients were noted to have hyperfibrinolytic activity, indicated by increasing D-dimer and decreasing fibrinogen. PI levels were not reported.

Solheim et al[7] reported that the Norwegian experience with Octaplas® did not reveal any issues with fibrinolysis during the period of 1993 – 2001, during which 208 liver transplants were performed using Octaplas®.

Since the introduction of OctaplasLG, which has an improved manufacturing process resulting in increased levels of PI, there have been no literature and/or pharmacovigilance reports of an increased incidence of hyperfibrinolysis during liver transplantation.

3. Risk of TRALI

TRALI is a leading cause of transfusion related mortality. The risk of TRALI is minimized with Octaplas™ because pooling of plasma dilutes neutrophil or HLA antibodies that may be contained in select donor units. No cases of TRALI have been reported in any of the submitted or published clinical studies, nor has any such relevant pharmacovigilance data been submitted to FDA. Current therapy with FFP, using only male donors, carries a risk of TRALI ~1:7,000 units to 1:20,000 units.[8]

8. Advisory Committee Meeting

The Octaplas BLA was presented to the Blood Products Advisory Committee (BPAC) on September 20, 2012. The questions posed to the Committee were as follows:

1. Do the data show that OctaplasLG is effective:
    a. For the management of preoperative or bleeding patients who require replacement of multiple coagulation factors?

b. As substitution of intentionally removed plasma (e.g. plasma exchange in patients with TTP)?

2. Do the data show that OctaplasLG has an acceptable safety profile for the indications stated in question 1?
3. If the answer to question 1 or question 2 is no, what additional studies should be performed premarketing for the proposed indications?
4. Please comment whether safety monitoring would be needed post-approval specifically to monitor:
   c. Thromboembolic events
   d. Excessive bleeding
   e. Transmission of HEV

The general consensus of the Committee was that the product was effective for the indications sought; however, there were safety concerns surrounding the product with high volume use and use in demanding clinical settings. This safety concern related mostly to the increased risk for hyperfibrinolysis due to lowered levels of alpha-2-plasmin inhibitor in the product, relative to FFP, particularly in the clinical setting of liver transplantation. The Committee recommended post-marketing evaluation of this safety issue.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

10. Labeling

The proposed proprietary name of the product, Octaplas™, was determined to be acceptable. A copy of an acceptable Full Prescribing Information is attached. Carton and container labels submitted to BLA amendment 38 were considered acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

It is recommended that Octaplas™ be approved for the proposed indications.

b) Risk/ Benefit Assessment

Use of Source Plasma

Octaplas™ will be manufactured from 630 – 1,520 units of Source Plasma and/or recovered plasma supplied by US licensed blood establishments and placed in the freezer within (b)(4) hr of blood draw. US Source Plasma has a higher viral marker rate when compared with recovered plasma from whole blood donations. This poses a theoretically increased risk for viral transmission when Source Plasma is used; however, this potential risk is mitigated by:

- Source Plasma blood establishment quality management in accordance with the International Quality Plasma Program (IQPP) standard of the Plasma Protein Therapeutics Association (PPTA) that governs donor qualification, quality assurance, donor deferral, education and training of personnel and viral marker monitoring; and
- Adventitious agents testing of individual units or mini-pools or manufacturing plasma

pools, as appropriate, using FDA licensed kits including nucleic acid amplification testing for HAV, HBV, HCV, HIV and an in-house validated NAT for HEV.

Furthermore, (b)(4) lots manufactured from Source Plasma have been distributed since 2006 in Europe and Canada without report of seroconversion or transfusion transmitted disease.

Viral Safety

Unlike plasma derivatives, Octaplas™ manufacture incorporates one viral inactivation step rather than two orthogonal, targeted steps in order to avoid potential damage to any of the multiple proteins in the product that are required for its safety and efficacy. The solvent/detergent treatment process results in adequate reduction factors for enveloped viruses such as HIV, HCV and HBV. The current risks for transmission of HIV and HCV infection with FFP are 1:1.4 million units and 1:1.1 million units respectively.[9] The risk for transmission of HBV infection with FFP is 1:280,000 to 1:357,000 units.[10] However, this calculated estimate for HBV transmission was performed prior to widespread nucleic acid testing (NAT) for HBV; therefore, the current risk is presumably lower.

Viral transmission of non-enveloped viruses is mitigated by:

- Control of viral load by NAT: only plasma pools negative for HAV and HEV, and that contain a maximum of 10.0 IU/μL of parvovirus B19 are accepted
- Immune neutralization based on specified minimum antibody levels against HAV and parvovirus B19

With regard to the risk for transmission of Hepatitis E Virus (HEV), the data on the burden in the plasma pool and the prevalence of antibodies in plasma donations and/or plasma pools is unavailable. However, mitigation of HEV transmission will be addressed similarly to HAV and parvovirus B19. A validated HEV NAT to control virus level in the manufacturing plasma pool has been implemented and a specified level of antibody against HEV in the final product will not be less than 0.2 IU/mL.

Transmission of CJD or vCJD

The risk of transmitting Creutzfeldt Jakob Disease (CJD) or variant Creutzfeldt Jakob disease through US sourced plasma is considered to be very low.

Thromboembolism and Hyperfibrinolysis

The following has been reported in patients who have received Octaplas:

- Thromboembolism (presumably due to low Protein S concentrations in Octaplas) in patients undergoing plasma exchange for TTP
- An increased incidence of hyperfibrinolysis (presumably due to low plasmin inhibitor concentrations in Octaplas) in patients undergoing liver transplantation

These are isolated reports involving small numbers of patients, and all patients received the predecessor product to the current version of Octaplas. The current version has an improved manufacturing process resulting in increased levels of Protein S that are within the lower limit of the reference range and increased levels of plasmin inhibitor which mitigate these risks. Further, Octapharma has agreed to postmarketing studies for each of these risks in the

respective clinical settings.

Conclusion

Each of the identified potential risks above is associated with a proposed mitigation strategy. Further, there is extensive experience showing reduction in risk of TRALI and TRALI related deaths with Octaplas (see Section 7.3). These data indicate that the likely benefit of TRALI reduction outweighs the potential risks with the product and exceeds the theoretical (i.e. to date undemonstrated) risk for transmission of CJD/vCJD from US sourced plasma.

Octaplas also benefits from a standardized dose of 200 mL plasma vs. 200 – 250 mL for FFP and the requirement to meet final release specifications for more consistent levels of coagulation proteins and inhibitors when compared to FFP (see Table 5).

c) Recommendation for Postmarketing Risk Management Activities

Octapharma's pharmacovigilance plan was reviewed and enhanced by FDA. In addition to Octapharma's proposals for routine passive surveillance for all serious and unexpected adverse events, FDA has enhanced the safety monitoring plan with 2 required studies to evaluate for the potential of excess risk of hyperfibrinolytic and thromboembolic events following Octaplas™ exposure, compared to fresh frozen plasma (see "Postmarketing Requirements under Section 505(o)" below). OBE and OBRR agree with the enhanced safety monitoring plan as described below.

	Health Outcome	**Octapharma Action Plan**
Important identified risks	1. Hypersensitivity and anaphylaxis 2. Venous thromboembolism	▪ Routine (passive) surveillance ▪ PMR Study LAS-214, "Non-interventional 2-arm study to evaluate the safety of Octaplas™ in patients treated for TTP with special emphasis on monitoring the occurrence of thromboembolic events (TEEs)"
Important potential risks	3. General virus safety 4. Hemolytic transfusion reaction 5. TRALI 6. Excessive bleeding due to hyperfibrinolysis 7. ABO-incompatible OctaplasLG transfusion	▪ Routine (passive) surveillance ▪ PMR Study LAS-215, "A non-interventional, open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients in ages <16 years old who require therapeutic plasma exchange"
Important missing information	8. Safety in pediatric, elderly and pregnant and nursing women	Routine (passive) surveillance

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The submission of pediatric studies is deferred until September 30, 2016 for study #1 below and until October 31, 2017 for study #2 below because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The deferred pediatric studies required under 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

1. An open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients <16 years old who require multiple plasma coagulation factors

   Final Protocol Submission: July 2013
   Study Completion Date: February 2016
   Final Report Submission: September 2016

2. A non-interventional, open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients <16 years old who require therapeutic plasma exchange

   Final Protocol Submission: August 2013
   Study Completion Date: March 2017
   Final Report Submission: October 2017

POSTMARKETING REQUIREMENTS UNDER 505(o)

The applicant has committed to the following:

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

An analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of thromboembolism in the TTP patient population and risk of hyperfibrinolysis in the liver transplantation patient population.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Clinical studies to further assess these potential risks are needed because Octaplas™ contains lower Protein S and alpha-2-plasmin inhibitor levels than found in FFP. The completed clinical studies are considered too small to reliably assess the potential for adverse events.

Therefore, based on appropriate scientific data, it was determined that the sponsor be required to conduct the following studies:

1. Non-interventional 2-arm study to evaluate the safety of Octaplas™ in patients treated for TTP with special emphasis on monitoring the occurrence of thromboembolic events

   Final Protocol Submission: August 2013
   Study Completion Date: December 2017
   Final Report Submission: July 2018

2. Non-interventional 2-arm study to evaluate the safety of Octaplas™ versus FFP in patients undergoing orthotopic liver transplantation with a special emphasis on hyperfibrinolysis

   Final Protocol Submission: October 2013
   Study Completion Date: April 2017
   Final Report Submission: November 2017

References:

1. Solheim BG, Hellstern P. Composition, efficacy, and safety of S/D-treated plasma. Transfusion 2003; 43:1176-1178.
2. Hellstern P, Sachse H, Schwinn H, Oberfrank K. Manufacture and characterization of a solvent/ detergent-treated human plasma. Vox Sang 1992; 63:178-185.
3. Yarranton H, Cohen H, Pavord SR, Benjamin S, Hagger D, Machin SJ. Venous thromboembolism associated with the management of acute thrombotic thrombocytopenic purpura. Br J Haematology 2003; 121:778-785.
4. Rizvi, MA, Vesely, SK, George, JN, Chandler, L, Duvall, D, Smith, Gilcher, RO. Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura–hemolytic–uremic syndrome. Transfusion 2000; 40:896–901.
5. de Jonge J., Groenland THN, Metselaar HJ, et al. Fibrinolysis during liver transplantation is enhanced by using solvent/detergent virus-inactivated plasma (ESDEP®). Anesth Analg 2002; 94:1127-31.
6. Magner JJ, Crowley KJ, Boylan JF. Fatal fibrinolysis during orthotopic liver transplantation in patients receiving solvent/detergent-treated plasma (Octaplas). J Cardiothorac Vasc Anesth 2007; 21(3):410-3.
7. Solheim B, Bergan A, Brosstad F, Innes R, Svennevig JL. Fibrinolysis during liver transplantation is enhanced by using solvent/detergent virus-inactivated plasma (ESDEP®). Anesth Analg 2003; 96:1230-1231.
8. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. Blood 2012; 119(7):1757-1767.
9. Zou S, Dorsey KA, Notari EP, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. Transfusion 2010; 50:1495-1504.
10. Zou S, Stramer SL, Notari EP, et al. Current incidence and residual risk of hepatitis B infection among blood donors in the United States. Transfusion 2009; 49:1609-1620.